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Outpatient Management of Sickle Cell Disease: Assessment of 13 Years Follow-Up of Pediatric Patients at the Sylvanus Olympio University Hospital

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Abstract

Objective: To evaluate thirteen years of ambulatory follow-up of patients with major forms of sickle cell disease. **Methods:** This was a study of 1055 records of sickle cell patients aged 6 months to 45 years followed between 2006 and 2018. **Results:** Six hundred and eighty-one (64.5%) homozygous SS, 283 (26.8%) SC, 86 (8.2%) SF, 4 (0.4%) Sß thalassemia and 1 (0.1%) SD sickle cell patients were followed. The majority of the patients (97.9%) were living in the capital city of Lomé and its surrounding suburbs. Most children (67.3%) were less than 5-year-old when they were diagnosed with sickle cell disease, and only 21.3% of cases were discovered before the first year birthday of the patients. Osteo-articular vaso occlusive crisis (VOC) was the principal symptom at the onset of the diagnosis, approximately 28.9% of the cases, followed by severe anemia (19%), then hand-foot syndrome in 15.6%. The systematic screening was performed in 5.4%. Twenty-six percent were G6PD deficient, 4 were HIV immunocompromised, and 29.7% were transfused. Among the degenerative complications, 2.4% had retinopathy, 1.9% osteonecrosis of the femoral head, 1.4% leg ulcers, and 0.8% cardiomyopathy. Salmonella typhi was the main cause of infection, 51.4% of the cases. The mean baseline hemoglobin level (n = 27) was 7.67 ± 1.64 g/dl. Four (0.4%) patients had a splenectomy. The mortality rate was 2.4%. The primary cause of death was anemia (28%), followed by sepsis in 20% of the cases. One case of suicide was documented as the cause of death. **Conclusion:** Outpatient medical follow-up of sickle cell patients is essential in sub-Saharan African countries where neo-

natal screening does not exist, and diagnosis is often late. The improvement in quality of life observed should be studied.

Keywords

Sickle Cell Disease, Outpatient Follow-Up, Lomé

1. Introduction

Sickle cell disease is the most common hemoglobinopathy in the world, affecting 10% to 40% of the African population. In most countries where it is a major concern, its management has remained inadequate. In these countries, it accounts for a significant proportion of the morbidity and mortality of children. Since May 2005, the World Health Organization (WHO) has added sickle cell disease to its list of public health priorities [1]. It recommends and encourages early medical follow-up, the benefits of which were first demonstrated in the United States and Jamaica, and then in France [2] [3] [4].

Indeed, the progress in the understanding of the pathophysiology of sickle cell disease, the results obtained in the early management and regular medical follow-up of sickle cell patients in Western countries have made it possible to improve their quality of life, prevent the early onset of complications and extend their life expectancy [5].

In Togo, the prevalence of sickle cell disease in all forms is estimated at 16% with 1% to 2.3% of the patients affected having the SS, SC, and S-beta thalassemia forms [6]. Ambulatory follow-up of sickle cell patients is practiced in the pediatric department of the Centre Hospitalier Universitaire Sylvanus Olympio (CHU SO). An evaluation of the first year of follow-up was done in 1999 by Gbadoé *et al.* [7].

The aim of this work is to evaluate thirteen (13) years of follow-up of sickle cell patients in the pediatric department of the CHU SO.

2. Patients and Method

2.1. Study Framework

This study was initiated by the sickle cell disease management section of the Hematology-Oncology unit of the pediatric department of the Centre Hospitalier Universitaire Sylvanus Olympio (CHU SO) in Lomé.

The pediatric department of the CHU Sylvanus Olympio has a capacity of 170 beds and cribs spread over ten hospitalization pavilions, including two continuing care pavilions. It is the national reference service for child healthcare in Togo. In the hierarchy of health structures in the country, the pediatric department is ranked as a mid-level. Each year, approximately nine thousand children from age 0 to 18 years seek medical care in the pediatric department, and a third of those patients are hospitalized. The hemato-oncology unit has an oncology subunit and a hematology subunit that house the sickle cell management section.

2.1.1. Description of the Sickle Cell Disease Management Section

About 1500 sickle cell children were followed on as the outpatient basis since 1996. On average 40 sickle cell patients came to the consultation each time.

2.1.2. Services

The Sickle Cell Management Unit offers outpatient follow-up consultations for sickle cell patients including children, adolescents, and young adults). The department offers a weekly consultation for sickle cell patients on Wednesdays between 3 and 7 pm. After the initial consultation, each patient continues with a follow-up every other month. Some patients were seen on appointment-based encounters. The sickle cell monitoring unit was part of the Infectiology and Onco-Hematology Unit. The average number of admissions to each consultation is estimated at 40 sickle cell patients. Each sickle cell patient has a medical record that remained in the unit, but a follow-up booklet was given to the patients to bring them on every encounter with health care professionals. A 24 hours medical assistance in case of acute complications is available for all sickle cell patients. In 1996 two pediatricians initiated these consultations. From 2004, more doctors joined the team and they have been an average of 2 - 4 consultation shifts every Wednesday by the added physicians.

2.2. Materials and Study Methods

2.2.1. Materials

Our work included 1055 cases of sickle cell disease (SS, SC, Sß thalassemia, SF, SD) followed up between January 2006 and December 2018.

2.2.2. Inclusion Criteria

We included in our study all SS, SC, SF, Sß thalassemia, and SD sickle cell patients (children, adolescents, and young adults) followed up between 2006 and 2018, with or without G6PD deficiency.

2.2.3. Non-Inclusion Criteria

We excluded from our study files patients with sickle cell trait AS, other hemoglobinopathy CC, AC, AF, isolated G6PD deficiencies, and files with almost no information.

2.2.4. Study Methods

This is a retrospective study of 1055 sickle cell patients followed up in the Infectious Diseases and Onco-Hematology Unit of the Pediatric Department of the CHU Sylvanus Olympio.

Our data were entered and processed in SPSS and Epi Data. We used the chi-square test at the 5% threshold for statistical analysis of qualitative data.

3. Results

3.1. Epidemiological Aspects

Over the period of 13 years (2006-2018), 1062 files of patients with sickle cell

disease were reviewed. Among those, 1055 files met the criteria for the study, and therefore they were retained for the study. In 7 files the medical records files were incomplete and rejected**.** Our study population represented 99.3% of registered patients.

The majority of patients were aged between 5 and 24 years. Those under 5 years of age represented 9.3% of the total number of patients (**Figure 1**). There were 566 (53.6%) male patients and 489 (46.4%) female patients with a sex ratio of 1.16. The sickle cell patients followed in our unit came from all 6 regions of Togo, Lomé—Commune (54.5%), Maritime (43.4%), Plateaux (1.5%), Kara (0.3%), Savanes (0.2%) and Central (0.1%).

3.2. Clinical Aspects

The age at the diagnosis was specified in 813 patients (77.1%). The average age was 5.4 ± 4.6 years. Only 21.3% were discovered before the age of 1 year. The circumstances of discovery were reported in 946 patients. Osteo-articular VOC was the first circumstance of discovery (28.9%), followed by decompensated anemia (19%) and hand-foot syndrome (15.6%). Only 5.4% of patients were discovered systematically. In 4% of cases, the discovery was made during a family investigation.

The mean age of the patients who were systematically screened was 14.1 ± 7.9 years. Of the 1055 sickle cell patients who followed up, SS homozygotes were in the majority (64.5%) followed by SC and Sβthalassemia (0.4%). For 8.2% of the patients, it was an SF profile. One patient had an SD profile.

Osteoarticular VOC was the primary finding in SS and SC forms of sickle cell disease (**Table 1**).

The initial assessment (**Table 2**) revealed that 26% of sickle cell patients with G6PD deficiency and 18% with cardiomegaly.

The distribution of patients according to the number of follow-up visits during the last 24 months revealed 190 patients who had attended at least one

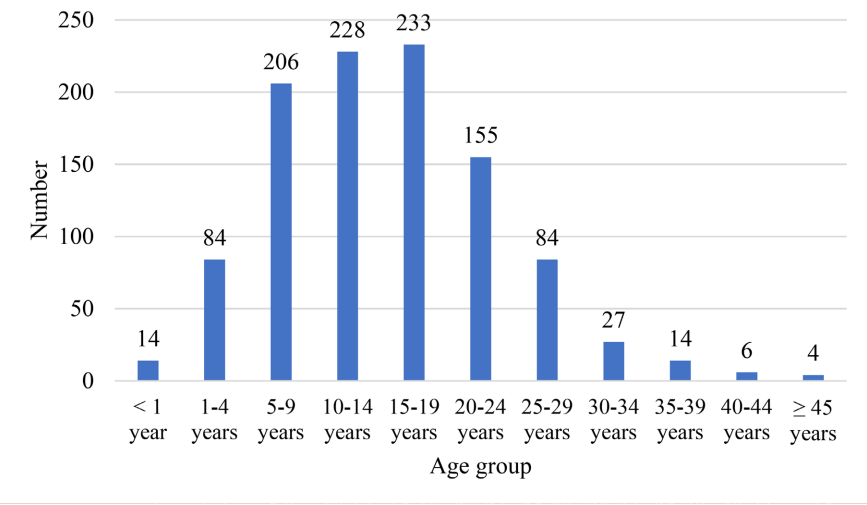

Figure 1. Distribution of patients by age.

Table 1. Distribution of patients according to SS or SC haemoglobin profile and circumstances of discovery.

	Hb SS		Hb SC		p
	n	%	n	%	
Osteoarticular VOC*	151	24.5	98	41.5	0.002
Anemia	138	22.4	26	11.0	0.000
Hand-foot syndrome	104	16.9	23	9.7	0.005
Infectious syndrome	95	15.4	30	12.7	0.577
Systematic screening	25	4.1	19	8.0	0.235
Abdominal VOC*	33	5.4	8	3.3	0.702
Splenomegalia	27	4.4	7	3.3	0.125
Family survey	20	3.2	15	6.3	0.449
Jaundice	23	3.7	10	4.2	0.972
Total	**616**	**100**	**236**	**100**	-

*Vaso-occlusive crisis.

Table 2. Distribution of patients according to the result of the initial assessment.

	Requested	Realized	Rate of achievement (%)	Pathological	
				n	%
Rhesus blood group	1055	1055	100	-	-
Determination of G_6PD	325	100	30.8	26	26.0
chest X-ray	288	194	67.4	35	18.0
Ophthalmology consultation	211	117	55.5	ND	ND
HBs Ag	173	90	52	6	6.7
Abdominal ultrasound	165	102	61.8	16	15.7
Electrocardiogram	143	92	64.3	49	53.3
Retinal angiofluorography	137	60	43.8	25	41.7
HIV serology	114	56	49.1	4	7.1
Cardiac ultrasound	89	49	55.1	8	16.3
Transcranial Doppler	1	0	0	ND	ND

appointment, 67 patients who had attended two appointments, and 118 patients who had attended three or more appointments. In the last 24 months, 95 patients had one emergency visit, 33 patients had two visits and 31 patients had three or more visits. Two hundred and thirty-two (232) hospitalizations were counted in the last 24 months for 140 patients, *i.e.* 1 hospitalization per patient per year.

The majority of the sickle cell patients followed (70.3%) had never been

transfused. Of those who were transfused, 24% were transfused less than twice. Among the complications found in sickle cell patients during the whole follow-up period, VOC represented 68%, infectious complications 35.7%, thrombotic complications 6.9%, chronic complications 9.3% and other complications 4.5% (Table 3). Anemic complications were not documented.

3.3. Evolutionary Aspects

Twenty-five (25) sickle cell patients died, representing a mortality rate of 2.4%. The causes of death were anemia (n = 7), sepsis (n = 5), acute chest syndrome/respiratory distress (n = 2), heart failure (n = 1), renal failure (n = 1), stroke (n = 1), suicide (n = 1), HIV/AIDS infection (n = 1) and severe VOC of

Table 3. Distribution of patients according to complications (n = 1055).

		Effectif	Percentage
Vaso-occlusive crisis (VOC)	Osteoarticular VOC	309	29.3
	Hand-foot syndrome	305	28.9
	Abdominal VOC	103	9.8
Infectious complications	Malaria	213	20.2
	Acute chest syndrome	52	4.9
	Acute osteomyelitis	47	4.5
	Chronic osteomyelitis	22	2.1
	Sepsis	18	1.7
	Urinary tract infection	13	1.2
	Acute bacterial meningitis	10	0.9
	Osteitis post Hand-foot syndrome	1	0.1
	Osteoarthritis of the hip	1	0.1
Thrombotic complications	Priapism	61	5.8
	Stroke	12	1.1
Chronic complications	Enuresis	34	3.2
	Retinopathy	25	2.4
	Osteonecrosis of the femoral head	20	1.9
	Leg ulcer	15	1.4
	Biliary lithiasis	10	0.9
	Cardiomyopathy	8	0.8
	Gross hematuria	3	0.3
	Nephrotic syndrome	3	0.3
Other complications	Dental caries	47	4.5
	Sexual impotence after priapism	1	0.1

undetermined etiology (n = 6). The mean age of the patients at death was 12.28 ± 6.66 years. The average number of deaths per year was 2.27 ± 0.90. Thirteen (13) male and 12 female sickle cell patients died. Of the 25 patients who died, 24 were SS homozygotes and one had a SF hemoglobin profile.

4. Discussion

Our study was exposed to some methodological biases. The observation book which was our data collection tool is a common book for all children in the pediatric's ward. It does not include a number of headings specific to sickle cell patients. The absence of these headings meant that this information was not systematically sought by all the doctors during the follow-up. This explains the lack of information in some files.

4.1. Epidemiological Aspects

The reorganization of the unit with the increase in the number of consultation posts and the various IEC activities carried out within the care section has made it possible to show the importance of the patients already being followed up who, by word of mouth, spread information on the quality of sickle cell disease care in the hospital. On the other hand, there has been renewed interest in sickle cell disease in the media since 2005, when the WHO devoted an agenda item to sickle cell disease and recommended several measures at its 59th annual congress [1].

Our study population not only was mainly pediatric-aged children but also some adolescents and young adults as in most pediatric chronic disease management units [8]. This can be explained by the difficulty that the patients have in leaving their pediatrician who seems to understand their problem better and who has been helping them to cope with their suffering for many years. Furthermore, in our hospital, there is no sickle cell unit for adults.

Adequate management of sickle cell disease must be early, therefore early screening must be encouraged especially in countries where there is no neonatal screening [1].

The male predominance found in our series has no particular explanation, especially since sickle cell disease is an autosomal disease.

Homozygous SS sickle cell patients were predominant in our series. In contrast, a study in Burkina Faso, among a population of newborns found that the prevalence of Hb C was 16.7% as opposed to 7.1% Hb S [9]. This can be explained by the fact that hemoglobin C originates in the Volta basin (Burkina Faso, northern Togo, and northern Ghana) [10].

4.2. Clinical Aspects

Sickle cell disease was discovered in 67.3% of our patients before the age of 5 years. Only 31.6% of those under 5 years of age were found before the age of 1 year and more than half (55.2%) were between 4 and 5 years of age. Ideally, newborn

screening should be carried out to ensure adequate treatment. But failing that, early detection is necessary. In the 1960s, John Dacie described sickle cell disease as an essentially pediatric disease, as the majority of deaths related to sickle cell disease occurred between the ages of 1 and 3 [11]. Despite the progress made in the management of the disease, the risk of premature death still exists. An estimated 5% of deaths in children under 5 years of age are related to sickle cell disease in Africa [1]. This proportion rises to 9% in West Africa and is as high as 16% in some countries. In Jamaica, the majority of deaths from sickle cell disease occur between 6 and 12 months of age [1]. The WHO estimates that half of all sickle cell patients die before the age of 5 years. As the mean age of diagnosis in our series is 5.4 ± 4.6 years, it is highly likely that many patients die without being diagnosed with sickle cell disease.

The mean age of systematic screening is even older (14.1 ± 7.9 years) and systematic screening only concerns 5.4% of our study population.

In most countries where sickle cell disease is a major public health concern, routine screening is not commonly practiced and the diagnosis is usually made when the patient presents with a serious complication [1].

Evidence suggests that newborn screening for sickle cell disease, when linked to timely diagnostic testing, parental education, and comprehensive care, can significantly reduce morbidity and mortality in the first year of life and in infancy [12].

The absence of neonatal screening in our series is due to the lack of a national policy incorporating a neonatal screening and follow-up program for sickle cell disease. This explains the late detection and management of the disease in most of our patients.

Sickle cell disease is usually discovered in Africa during complications, and in our series, osteoarticular VOC were the first circumstances of discovery in both homozygous SS and SC types of sickle cell disease. The VOC were followed by anemia and hand-foot syndrome. These first 3 circumstances of discovery were significantly more related to homozygous sickle cell disease SS than to SC. For the other circumstances of discovery, including abdominal CVO, there was no difference between the 2 sickle cell genotypes.

Our results are contrary to those of Ayéroué *et al.* in Burkina Faso who compared SS sickle cell patients to SC sickle cell patients and found that VOC were equivalent in mean number per year and mean duration per year. Regarding anemia, they also found that it was more frequent in SS than in SC [9].

CVO was also the first type of complication found in our patients. Shapiro *et al.* had already reported the high frequency of CVO in sickle cell patients, estimated at 30% of pain days in a year [13]. Paul Telfer *et al.* found similar results [14].

Malaria ranked second in our series whereas Paul Telfer *et al.* ranked chest syndrome second [14]. This difference is related to the endemicity of malaria in our part of Africa and the vulnerability of sickle cell patients to this condition whereas sickle cell traits would be protected. In the African series, the first reason

for the consultation has always been VOC, followed by infectious and anemic complications [7] [15].

Priapism was the third most common complication in our patients (5.8%). Since 1934, priapism has been recognized as a complication of sickle cell disease [16]. In our unit, Gbadoé *et al.* found a prevalence of 26.3% in 2001 [7]. Our prevalence is much lower than that of Gbadoé *et al.* whose figure is probably closer to reality as it was based on the interview of each patient. As priapism is a complication that often occurs at night and is managed outside the follow-up unit, episodes were not always noted in the medical record. Sickle cell disease is responsible for 65% of priapisms in children [17].

In our study, salmonella was the most common germ found in infections. This is a germ often found in sickle cell patients [18].

Determination of the baseline hemoglobin level is of vital importance in sickle cell disease. Its knowledge allows the practitioner to judge the evolution of the disease from the various blood count controls and, in case of anemia, to indicate or not a blood transfusion. Unfortunately, this level was only determined in 27 of our patients and was on average 7.67 ± 1.64g/dl. This level is similar to the 1999 study by Gbadoé *et al.* in SS homozygous patients (7.4 ± 1.4 g/dl) but is far from that of the SC type found by the same authors (10.7 ± 2.4 g/dl) [7]. The baseline hemoglobin level was reported to be higher in the order of 10 to 12 g/dl in the Senegal haplotype [19]. This indicates the severity of the signs in the benign haplotype. The low rate of hospitalization of our patients in the last 24 months, on average one hospitalization per patient per year, is a good reflection of the importance of follow-up.

The mean age of our patients at death was 12.3 ± 6.7 years. The lack of neonatal screening means that many children with sickle cell disease die without access to follow-up units. Half of all sickle cell patients die before the age of 5 [1] [20]. In our series, as in all the others, anemia and infection were the main causes of death.

We had registered death in children under 5 years of age, unlike Paul Telfer *et al.* in England who had no deaths in the same age group [14]. In their series, this was due to neonatal screening and early management, as this follow-up program was absent in our series.

5. Conclusion

Reducing mortality from sickle cell disease requires easy access to care and regular monitoring of sickle cell patients. In the absence of a neonatal diagnosis, the early diagnosis must be promoted. The disease remains fraught with complications in patients in sub-Saharan Africa. A study comparing the different periods of follow-up will help to better demonstrate its benefits.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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